Safety and Tolerability of Linagliptin in Patients With Type 2 Diabetes: A Comprehensive Pooled Analysis of 22 Placebo-controlled Studies

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ABSTRACT

Purpose: Dipeptidyl peptidase (DPP)-4 inhibitors are an increasingly used antihyperglycemic therapy for patients with type 2 diabetes mellitus (T2DM). Linagliptin, an orally administered DPP-4 inhibitor, has demonstrated favorable efficacy/safety in clinical trials. The aim of this post hoc pooled analysis was to expand current knowledge of the safety of linagliptin.

Methods: Safety data for once-daily linagliptin 5 mg (1 study of linagliptin 2.5 mg twice daily) were analyzed from 22 randomized, double-blind, Phase I–III, placebo-controlled clinical trials of ≤102 weeks' duration. Assessments of pooled data included incidence of patient-reported adverse events (AEs).

Findings: Data from 7400 patients (linagliptin, 4810; placebo, 2590) were pooled. Most patients (58.4%) had T2DM diagnosis for >5 years; approximately 75% were receiving ≥1 type of background therapy in addition to linagliptin/placebo. Overall exposure to the study drug was 2412.8 years for linagliptin and 1481.4 years for placebo (mean [SD], 183 [120] days and 209 [150] days, respectively). Overall frequencies of AEs were similar for linagliptin- and placebo-treated patients (57.3% and 61.8%, respectively). The incidence of neoplastic AEs was low (0.6% and 0.9%, respectively); there were no reports of pancreatic neoplasia. Pancreatitis was observed in 2 linagliptin-treated patients (<0.1%) and 1 placebo-treated patient (<0.1%). The occurrence of cardiac disorder AEs was similar in linagliptin- and placebo-treated patients (3.2% [n = 153] and 3.3% [n = 83], respectively); the incidence of heart failure AEs for linagliptin- and placebo-treated patients was 0.2% (n = 11) and 0.3% (n = 7), respectively. Overall, linagliptin was weight neutral. Occurrence of investigator-defined hypoglycemic AEs was low for both linagliptin and placebo (11.5% vs 14.0%). In patients receiving concomitant sulfonylurea therapy, investigator-defined hypoglycemic AEs were more frequent with linagliptin versus placebo (22.1% [238/1079] vs 14.5% [61/421], respectively). Subgroup analyses showed similar frequencies of AEs for linagliptin- and placebo-treated patients across different age groups and renal function levels.

Implications: This updated and expanded pooled, post hoc analysis of 22 placebo-controlled trials of linagliptin 5 mg daily supports previous findings of the acceptable overall safety/tolerability profile of linagliptin when administered to a broad range of patients with T2DM. Linagliptin-treated patients demonstrated a low overall risk of hypoglycemia (risk increased by concomitant sulfonylurea therapy). As with all pooled analyses, this study is limited by the use of data from different studies, and the relatively short duration of some included studies, although use of individual patient data from consistently designed trials should minimize methodological differences between trials. Results from ongoing clinical trials will provide additional insight into the long-term safety/tolerability of linagliptin. (*Clin Ther.* 2014;36:1130–1146) © 2014 The Authors. Published by Elsevier HS Journals, Inc.

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INTRODUCTION

The growing global burden of type 2 diabetes mellitus (T2DM) has led to an ongoing search for treatments that demonstrate both efficacy and safety in the management of this chronic condition. Dipeptidyl peptidase (DPP)-4 inhibitors are becoming important oral antihyperglycemic agents, a recommended therapeutic option when glycemic control cannot be achieved with metformin or first-line therapy where metformin is contraindicated.[1] Treatment with DPP-4 inhibitors leads to improvements in glycemic control, with a low risk of hypoglycemia, if used in combination with agents that are not associated with an increased risk of hypoglycemia during monotherapy.[2]

Linagliptin is a once-daily, orally administered DPP-4 inhibitor with a xanthine-based structure[3,4] and exhibits high-affinity binding to DPP-4 in plasma and tissues,[5] resulting in only a small fraction of the drug being unbound. These features account for the long terminal half-life (>100 hours) and nonlinear pharmacokinetic profile of linagliptin.[4,6,7] One clinically important feature is its largely nonrenal route of elimination (80% hepatic vs 5% renal),[6,8,9] which means that, in contrast to most other DPP-4 inhibitors,[10] dose adjustment of linagliptin is not required in patients with renal impairment.[11] The glucose-lowering efficacy of linagliptin is based on its impact on the incretin hormones, active glucagon-like peptide (GLP)-1, and gastric inhibitory peptide (GIP), which are secreted from the intestine after a meal. In the presence of hyperglycemia, these hormones promote glucose-dependent insulin secretion and reduce glucagon secretion.[12] Both active GLP-1 and GIP are rapidly inactivated through cleavage by DPP-4.[13] Thus, the antihyperglycemic activity of linagliptin results from enhancement of the incretin effect. Inhibition of DPP-4 by linagliptin leads to an approximately 3-fold increase in active GLP-1 levels,[14,15] resulting in improvements in glycemic control in patients with T2DM.

Linagliptin has been evaluated in a clinical Phase I–III trial program in >40 countries and established a low overall rate of adverse events (AEs) that is similar to placebo, including a low incidence of hypoglycemia and a weight-neutral effect.[16–19] Several of the trials had a duration of 1 year or longer.[20–22] In 2012, a pooled analysis of linagliptin safety data from 8 randomized, double-blind, placebo-controlled Phase III clinical trials lasting ≤24 weeks demonstrated that linagliptin was well tolerated.[23]

The aim of the present post hoc analysis is to update the safety profile for linagliptin with all currently available placebo-controlled trials, now including clinical trials with a duration of as long as 102 weeks. The rationale for including only placebo-controlled trials was to avoid as much as possible confounding by the safety profiles of comparator therapies on the occurrence of AEs in the comparator arm. This analysis also includes an assessment of safety in 2 vulnerable patient populations—the elderly and patients with renal impairment.

PATIENTS AND METHODS

Patient Population

Safety data for once-daily linagliptin 5 mg (and 1 study [NCT01012037] that included patients receiving 2.5 mg twice daily) were analyzed for patients who participated in 1 of 22 randomized, double-blind, Phase I–III placebo-controlled clinical trials of up to 102 weeks' duration.[4,7,16–19,24–40] All studies were conducted in accordance with Good Clinical Practice guidelines and the principles of the Declaration of Helsinki.

Assessments

Safety and tolerability assessments included the incidence and severity of patient-reported AEs. These AEs were recorded by investigators and coded using the Medical Dictionary for Regulatory Activities (MedDRA) Version 15.1 as preferred terms grouped under individual system organ classes. Investigator-defined hypoglycemic AEs were based on both clinical symptoms and laboratory measurement of plasma glucose levels (as defined in the legend to **Figure**). Electrocardiograms, physical examinations, vital signs, and clinical and laboratory parameters were also reported. All laboratory assessments were performed by central laboratories.

Patient-level safety data were analyzed for the overall population and for subgroups based on age (<65, 65 to <75, and ≥75 years), renal function (estimated glomerular filtration rate <60, 60 to <90, and ≥90 mL/min/1.73 m^2, as determined by the Modified Diet in Renal Disease study equation), concomitant sulfonylurea (SU) treatment, and body mass index (<25, 25 to <30, and ≥30 kg/m^2).

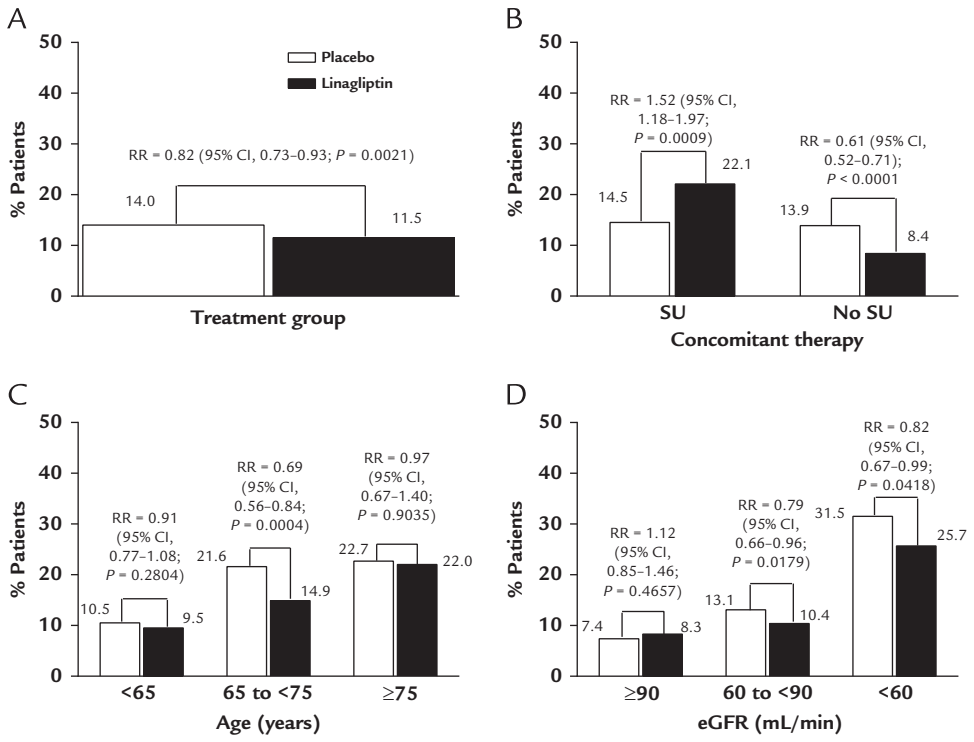

Figure. Percentage of patients with investigator-defined hypoglycemic adverse events. In the overall population (A), with or without concomitant sulfonylurea therapy (B), by age (C), and by renal function (dataset: patients treated with linagliptin 5 mg once daily or placebo and with data on estimated glomerular filtration rate [eGFR] [Modified Diet in Renal Disease] [N = 7375]) (treated set) (D). Hypoglycemic episodes were classified by investigators as asymptomatic if not accompanied by typical symptoms of hypoglycemia but with a measured plasma glucose concentration ≤3.9 mmol/L (≤70 mg/dL), documented symptomatic when a measured plasma glucose concentration ≥3.0 mmol/L (≥54 mg/dL) and ≤3.9 mmol/L (≤70 mg/dL) was accompanied by typical symptoms of hypoglycemia, documented symptomatic when a measured plasma glucose concentration <3.0 mmol/L (<54 mg/dL) was accompanied by typical symptoms of hypoglycemia without the need for external assistance, or severe when the assistance of another person was required to actively administer carbohydrate, glucagon, or other resuscitative actions. 95% CI, Fisher exact test *P* value. RR = relative risk.

Data Analysis

Analyses were conducted on individual patient data in the treated set (TS), which was defined as all patients who received at least 1 dose of the study drug. Data obtained after initiation of glycemic rescue were also included in the analysis.

Pooled safety data were analyzed using descriptive statistical methods to calculate AE incidence rates for the overall population and for the patient subgroups of interest. In an exploratory analysis, we assessed the influence of treatment on investigator-defined hypoglycemic AEs (for full definition, see the legend to Figure) overall and for the following categories of age, renal function, and use of SU expressed as relative risk with the corresponding 95% CIs. No other inferential statistical tests were conducted.

RESULTS

Patient Disposition, Baseline Characteristics, and Exposure

This post hoc pooled analysis included patients from all currently available placebo-controlled trials, for which data for both linagliptin and placebo groups on matched background therapy were available: a total of 7400 patients, of whom 4810 received linagliptin and 2590 received placebo (Table I).

Patients in the linagliptin- and placebo-treated groups had similar baseline demographic and clinical characteristics (Table II). For the overall dataset, the mean (SD) age was 58.5 (10.6) years, mean (SD) baseline glycosylated hemoglobin was 8.2% (0.9), and mean (SD) fasting plasma glucose was 9.1 mmol/L (2.5) (164.5 mg/dL [45.5]). The majority of patients (58.4%) had a diagnosis of T2DM for over 5 years. Approximately 13% of patients had a history of coronary artery disease at baseline (12.1% in the linagliptin group and 14.7% in the placebo group), and nearly two thirds were hypertensive (61.5% and 63.1%, respectively). Almost three fourths of patients were receiving antihypertensive therapy at the start of the trial (60.7% and 63.9%, respectively), the most frequent antihypertensive therapy being angiotensin-converting enzyme inhibitors (26.1% and 28.4%, respectively), and almost half were receiving lipid-lowering drugs (41.5% and 45.3%, respectively). Heart failure was present in a small minority of patients at baseline (1.5% and 1.6%, respectively). More than one fourth of patients had microvascular disease at baseline (26.1% and 31.0%, respectively).

During therapy, 1136 (23.6%) of linagliptin- and 650 (25.1%) of placebo-treated patients received no background antidiabetes medication; ~75% of the pooled population were receiving ≥1 type of background therapy in addition to linagliptin or placebo. The most frequent background therapies (alone or with other antidiabetes therapies) were insulin, SU, and metformin (patients receiving ≥1 background therapy could be included in ≥1 count) (Table II): a total of 1614 patients (21.8%) were receiving background treatment with insulin, 1500 (20.3%) were receiving SU therapy, and 4359 (58.9%) were receiving metformin. During the trial, more patients in the placebo group were receiving insulin background therapy (31.0%) than in the linagliptin group (16.9%), whereas more patients in the linagliptin group were receiving background SU therapy (22.4%) than in the placebo group (16.3%) (Table II).

Overall exposure to the study drug was 2412.8 years for the linagliptin group and 1481.4 years for placebo (mean [SD], 183 [120] days and 209 [150] days, respectively). Nearly two thirds of patients received treatment for at least 24 weeks (3117 [64.8%] and 1670 [64.5%], respectively).

Adverse Events

Overall frequencies of AEs were similar in linagliptin- and placebo-treated patients, with or without background treatment (57.3% and 61.8%, respectively) (Table III). The frequencies of serious AEs were also similar for linagliptin- and placebo-treated patients (4.8% and 6.4%, respectively) as were drug-related AEs (11.7% and 13.7%, respectively).

All AEs that occurred with a frequency of >2% for either linagliptin- or placebo-treated patients (or were AEs of interest) are shown in Table IV. The incidence of all infection and infestation AEs observed with linagliptin was 21.3% versus 25.0% with placebo, with nasopharyngitis reported in 5.8% and 6.0% of patients treated with linagliptin and placebo, respectively. Gastrointestinal disorders occurred in 11.4% of linagliptin- and 12.7% of placebo-treated patients; with similar incidences irrespective of whether patients were receiving no oral background therapy (linagliptin, 10.5% and placebo, 11.3%) or receiving concomitant therapy such as metformin or SU (linagliptin, 11.6% and placebo, 13.3%). Diarrhea was the only gastrointestinal AE that occurred at a frequency of ≥2% (2.7% and 3.0% for linagliptin- and placebo-treated patients, respectively).

The overall incidence of neoplasia (benign and malignant) was low –0.6% for linagliptin- and 0.9% for placebo-treated patients— and there were no reports of pancreatic neoplasia (Table IV). In the trials included in this analysis, pancreatitis was observed in 2 linagliptin-treated patients (<0.1%) and 1 placebo-treated patient (<0.1%). Corresponding figures for chronic pancreatitis were 3 patients (0.1%) in the linagliptin group, who reported exacerbation of pre-existing chronic pancreatitis, and none for patients receiving placebo. The pancreatitis episodes reported in the linagliptin group were all mild or moderate in intensity, and the episode reported for the patient receiving placebo was severe; none of the pancreatitis cases were fatal. Three of the 5 patients with recorded episodes of pancreatitis in the linagliptin group had episodes that were recorded as nonserious, whereas 2 additional patients required hospitalization; the patient with an episode of pancreatitis in the placebo group also required hospitalization. Increased blood amylase levels were reported in a similar proportion of linagliptin-treated patients (14 patients, 0.3%) and placebo-treated patients (4 patients, 0.2%).

The overall incidence of cardiac disorders was similar for linagliptin- and placebo-treated patients

Table I. Randomized, double-blind, placebo-controlled trials included in this pooled analysis.

ClinicalTrials.gov Registration Number	Background Treatment	Treatment Arms*	Duration (wk)	Mean Age (y)	Men (%)	White/ Asian (%)	Reference
	None	Linagliptin 1 mg once daily, n = 9 Linagliptin 2.5 mg once daily, n = 9 **Linagliptin 5 mg once daily, n = 8** Linagliptin 10 mg once daily, n = 9 **Placebo, n = 12**	<2	56	100	100.0/0	Heise et al[4]
	None	Linagliptin 2.5 mg once daily, n = 26 **Linagliptin 5 mg once daily, n = 16** Linagliptin 10 mg once daily, n = 19 **Placebo, n = 16**	4	62	94	100.0/0	Forst et al[7]
NCT00328172	None	Linagliptin 0.5 mg once daily, n = 58 Linagliptin 2.5 mg once daily, n = 57 **Linagliptin 5 mg once daily, n = 55** **Placebo, n = 67** Metformin, n = 65	12	57	57.9	90.1/3.6	Singh-Francot et al[30]
NCT00309608	Metformin (most received ≥1500 mg/d)	Linagliptin 1 mg once daily, n = 65 **Linagliptin 5 mg once daily, n = 66** Linagliptin 10 mg once daily, n = 66 **Placebo, n = 71** Glimepiride 1–3 mg once daily, n = 65	12	60	58.0	99.0/1.0	Forst et al[29]
NCT00641043	None	**Linagliptin 5 mg once daily + pioglitazone 30 mg once daily, n = 259** **Placebo + pioglitazone 30 mg once daily, n = 130**	24	57.5	60.9	74.6/24.9	Gomis et al[17]
NCT00621140	None	**Linagliptin 5 mg once daily, n = 336** **Placebo, n = 167**	24	55.7	48.3	53.7/46.1	Del Prato et al[16]
NCT00601250	Metformin (≥1500 mg/d or maximal tolerated dose)	**Linagliptin 5 mg once daily, n = 523** **Placebo, n = 177**	24	56.5	54.1	76.1/20.9	Taskinen et al[19]
NCT00602472	Metformin (≥1500 mg/d or maximal tolerated dose) + sulfonylurea	**Linagliptin 5 mg once daily, n = 792** **Placebo, n = 263**	24	58.1	47.2	46.6/51.7	Owens et al[18]
NCT00654381	None	Linagliptin 5 mg once daily, n = 159 Linagliptin 10 mg once daily, n = 160 Voglibose 0.2 mg TID, n = 162 Placebo, n = 80	12†	60.0	70.4	0.0/100.0	Kawamori et al[25]
NCT00819091	Sulfonylurea	Linagliptin 5 mg once daily, n = 157 Placebo, n = 81	18	56.9	52.7	43.7/48.6	Lewin et al[26,‡]
NCT00954447	Basal insulin alone or in combination with metformin and/or pioglitazone	**Linagliptin 5 mg once daily, n = 628** **Placebo, n = 627**	52§	59.7	52.2	N/A	Yki-Järvinen et al[31,‡]
NCT00716092	None	**Linagliptin 5 mg once daily, n = 40** Sitagliptin 100 mg, n = 41 **Placebo, n = 40**	4	61.1	50.5	N/A	Rauch et al[28]

(continued)

Table I. (continued).

ClinicalTrials.gov Registration Number	Background Treatment	Treatment Arms*	Duration (wk)	Mean Age (y)	Men (%)	White/ Asian (%)	Reference
NCT00800683	Existing glucose-lowering background therapy	**Linagliptin 5 mg once daily, n = 67** **Placebo, n = 63**	52	64.4	60.2	73.7/14.3	McGill et al[32,‡]
NCT00798161	None	**Linagliptin 5 mg once daily, n = 142** Metformin 500 mg BID, n = 144 Linagliptin 2.5 mg BID + metformin 500 BID, n = 143 Metformin 1000 mg BID, n = 147 Linagliptin 2.5 mg BID + metformin 1000 BID, n = 143 **Placebo, n = 72**	24	55.3	57.1	66.8/32.5	Haak et al[40]
NCT00740051	None	**Linagliptin 5 mg once daily, n = 151** **Placebo, n = 76**	18	56.5	38.8	70.6/27.4	Barnett et al[24]
NCT00996658	Metformin + pioglitazone	**Linagliptin 5 mg once daily, n = 183** **Placebo, n = 89**	24	53.8	48.5	31.2/68.8	Bajaj et al[33]
NCT01012037	Metformin (≥1500 mg/d or maximal tolerated dose)	**Linagliptin 2.5 mg BID, n = 223** **Linagliptin 5 mg once daily, n = 224** **Placebo, n = 44**	12	58.6	57	65.4/33.8	Ross et al[34]
NCT01084005	Metformin and/or sulfonylurea and/or basal insulin	**Linagliptin 5 mg once daily, n = 162** **Placebo, n = 79**	24	74.9	68.5	96.7/2.1	Barnett et al[35]
NCT01087502	Existing glucose-lowering background therapy	**Linagliptin 5 mg once daily, n = 113** **Placebo, n = 122** (weeks 1–12, then switched to glimepiride, 1–4 mg once daily until week 52)	52	67	N/A	N/A	Laasko et al[36]
NCT01215097	Metformin	**Linagliptin 5 mg once daily, n = 205** **Placebo, n = 100**	24	55.5	49.8	0.0/100.0	Wang et al[38]
NCT01214239	None	**Linagliptin 5 mg once daily, n = 200** **Placebo, n = 99**	24	N/A	N/A	0/100	Chen et al[37]
NCT01194830	Existing glucose-lowering background therapy	**Linagliptin 5 mg once daily, n = 101** **Placebo, n = 115**	24	54	54	0/0	Thrasher et al[39,‡]

N/A = not available; BID = twice daily; TID = three times daily.

*Only data from the treatment arms shown in bold were included in the pooled safety analysis reported here.

†The study duration was a total of 52 weeks, comprising an initial 12-week, placebo-controlled, double-blind phase, followed by a further 14 weeks of double-blind, active-controlled treatment, and then a 26-week open-label extension; data shown are from patients receiving linagliptin 5 mg or placebo in the initial 12 weeks of treatment.

‡Results from certain centers were later excluded due to serious noncompliance.

§The study duration was at least 52 weeks. Patients who had been randomly assigned early in the study were to be treated for longer than 52 weeks until the study close out, which was to occur as soon as all patients had been treated for at least 52 weeks.

Table II. Baseline demographic and clinical characteristics for pooled patients (TS).

	Linagliptin	Placebo
No. of patients	4810	2590
Sex, no. (%)		
Male	2575 (53.5)	1427 (55.1)
Female	2235 (46.5)	1163 (44.9)
Race, no. (%)		
White	2729 (56.7)	1537 (59.3)
Black	193 (4.0)	188 (7.3)
Asian	1888 (39.3)	865 (33.4)
Age, y	58.3 (10.6)	58.8 (10.5)
Age groups, y, no. (%)		
≤50	1082 (22.5)	546 (21.1)
51–65	2307 (48.0)	1243 (48.0)
65 to <75	1153 (24.0)	647 (25.0)
≥75	268 (5.6)	154 (5.9)
Weight, kg	79.6 (18.3)	82.0 (18.4)
Baseline BMI, kg/m^2	29.1 (5.2)	29.7 (5.3)
Baseline BMI, kg/m^2, no. (%)		
<30	2946 (61.2)	1444 (55.8)
≥30	1864 (38.8)	1146 (44.2)
Baseline eGFR (MDRD staging), mL/min, no. (%)		
≥90	1918 (39.9)	955 (36.9)
60 to <90	2263 (47.0)	1198 (46.3)
30 to <60	508 (10.6)	310 (12.0)
<30	111 (2.3)	112 (4.3)
Missing	10 (0.2)	15 (0.6)
Baseline Hb_{A1c}, %[*]	8.17 (0.88)	8.20 (0.90)
Fasting plasma glucose, mmol/L[*]	9.1 (2.5)	9.2 (2.6)
Fasting plasma glucose, mg/dL	164.2 (44.7)	165.1 (47.1)
Duration of diabetes, y, no. (%)		
≤1	631 (13.1)	292 (11.3)
>1 to ≤5	1440 (29.9)	701 (27.1)
>5	2731 (56.8)	1590 (61.4)
Missing	8 (0.2)	7 (0.3)
Relevant medical history at baseline, no. (%)		
Coronary artery disease	583 (12.1)	381 (14.7)
Cerebrovascular disease	187 (3.9)	130 (5.0)
Congestive heart failure	73 (1.5)	41 (1.6)
Hypertension	2958 (61.5)	1635 (63.1)
Microvascular disease[†]	1255 (26.1)	804 (31.0)
Patients receiving CV medication at baseline, no. (%)[‡]		
Antihypertensives	2920 (60.7)	1654 (63.9)
ACE inhibitors	1254 (26.1)	736 (28.4)
ARBs	717 (14.9)	398 (15.4)
β-Blockers	952 (19.8)	590 (22.8)

(continued)

Table II. (continued).

	Linagliptin	Placebo
Calcium antagonists	824 (17.1)	472 (18.2)
Diuretics	742 (15.4)	497 (19.2)
Combinations	531 (11.0)	290 (11.2)
Other	10 (0.2)	8 (0.3)
Lipid-lowering drugs	1994 (41.5)	1173 (45.3)
P-glycoprotein or CYP 3A inhibitors	168 (3.5)	108 (4.2)
Patients receiving antidiabetes background medication during treatment, no. (%)		
0	1136 (23.6)	650 (25.1)
1	2044 (42.5)	996 (38.5)
≥2	1630 (33.9)	944 (36.4)
Insulin ± other antidiabetes drug§	788 (16.4)	796 (30.7)
SU ± other antidiabetes drug§	1056 (22.0)	414 (16.0)
Insulin + SU ± other antidiabetes drug§	23 (0.5)	7 (0.3)
Metformin ± other antidiabetes drug§	2943 (61.2)	1416 (54.7)

Data are mean (SD) unless otherwise stated.
ACE = angiotensin-converting enzyme; ARBs = angiotensin II receptor blockers; BMI = body mass index; CV = cardiovascular; CYP 3A = cytochrome P-450 3A; eGFR = estimated glomerular filtration rate; Hb_{A1c} = glycosylated hemoglobin; MDRD = Modification of Diet in Renal Disease; SU = sulfonylurea; TS = treated set.
*Fasting plasma glucose data converted from mg/dL to mmol/L using conversion factor of 0.0555.
†Microvascular disease includes diabetic retinopathy, nephropathy, and neuropathy.
‡Patients were permitted to take >1 CV medication, if required.
§Patients receiving >1 background therapy could be included in >1 count.

(3.2% [n = 153] and 3.3% [n = 83], respectively) (Table IV). There was no apparent imbalance in heart failure AEs (based on the preferred terms *cardiac failure*, *cardiac failure acute*, and *cardiac failure congestive*) among linagliptin-treated patients compared with placebo-treated patients (0.2% [n = 11] and 0.3% [n = 7], respectively). These data equate to an incidence rate (per 1000 patient-years) of 0.45 for linagliptin and 0.46 for placebo. A total of 8 of 11 patients receiving linagliptin experienced heart failure that was recorded as being serious, 1 of which was fatal, compared with 3 of 7 patients receiving placebo (no fatal events). For the narrow standardized MedDRA query of cardiac failure (code 20000004) (Table IV), the incidence was 0.4% (n = 21) and 0.3% (n = 8) for linagliptin and placebo, respectively. Tachycardia (measured by counting the pulse and based on AE reporting) occurred at a similar frequency among linagliptin- and placebo-treated patients (0.2% and 0.1%, respectively) as did the reported AEs of arrhythmia (both 0.1%) and hypertension (2.3% and 2.8%, respectively). Ischemic cardiac events defined using MedDRA version 15.1 also occurred at levels <1.0% and at similar rates for linagliptin- and placebo-treated patients (Table IV).

Hepatobiliary AEs were reported infrequently for both the linagliptin and placebo groups (both 0.9%). Renal and urinary AEs were reported with a similar frequency for both the linagliptin and placebo groups (3.5% and 4.4%, respectively).

Overall, linagliptin was weight neutral, with no evidence of an increased incidence of AE reports of weight gain with linagliptin versus placebo (both 0.2%).

Hypoglycemia

The overall proportion of patients experiencing investigator-defined hypoglycemic AEs was significantly lower for linagliptin (11.5%) versus placebo (14.0%) (Figure A). This equated to an exposure-adjusted incidence rate (per 1000 patient-years) of

Table III. Frequency of AEs among patients who received linagliptin or placebo (TS).

AEs	Linagliptin (n = 4810)	Placebo (n = 2590)
Any AE	2758 (57.3)	1601 (61.8)
Drug-related AEs	562 (11.7)	354 (13.7)
AEs leading to discontinuation of trial drug	141 (2.9)	107 (4.1)
Serious AEs*	230 (4.8)	167 (6.4)
Fatal AEs	10 (0.2)	9 (0.3)

AE = adverse events; TS = treated set.
Data are number (%).
*Serious AEs that were considered to be drug-related: 13 (0.3%) and 3 (0.1%), for linagliptin and placebo, respectively.

25.5 and 28.1, respectively. The proportion of patients experiencing severe hypoglycemia, requiring assistance, was similar in both groups (linagliptin, 0.4%; placebo, 0.5%). However, it should be noted that the percentage of patients receiving background therapy with SU or insulin (± other antidiabetes therapies) was slightly greater among placebo-treated patients (1210, 46.7%) than linagliptin-treated patients (1844, 38.3%) (with similar percentages receiving both SU + insulin [± other antidiabetes therapies] in both groups [0.3% and 0.5%, respectively]) (Table II). Furthermore, the percentage of patients who received antidiabetic rescue medication during the study was approximately twice as high in the placebo group (22.3%) compared with those receiving linagliptin (10.5%).

Of the 553 patients receiving linagliptin who reported an investigator-defined hypoglycemic AE, 43.0% (238) were receiving concomitant SU therapy. Among patients receiving concomitant SU therapy, investigator-defined hypoglycemic AEs were more frequent, occurring in 22.1% (238/1079) of linagliptin- and 14.5% (61/421) of placebo-treated patients (Figure B). In contrast, the incidence of investigator-defined hypoglycemic AEs for linagliptin- and placebo-treated patients was similar for those receiving insulin during the treatment phase: 35.5% (288/811) and 36.0% (289/803), respectively, with a risk ratio of hypoglycemia for linagliptin versus placebo of 0.99 (95% CI, 0.87–1.21; $P = 0.8762$).

Subgroup Analyses

Analyses of the effect of age on the safety of linagliptin showed that treatment was well tolerated across all age groups, with a low incidence of investigator-defined hypoglycemic AEs (Table V). The overall incidence of AEs and AEs by system organ class was similar for linagliptin and placebo. As expected, advancing age was associated with a numerical increase in the incidence of AEs, but the incidences of AEs, including fatal events, for patients receiving linagliptin and placebo remained similar (Table V, Figure). Similarly, there was a small age-related increase in the frequency of cardiac ischemic events and heart failure, although the number of events was small, and frequencies were similar for linagliptin- and placebo-treated patients. A similar pattern was observed for the incidence of hypoglycemic events by age (Figure C).

Analyses of safety data by renal function showed that linagliptin was associated with a similar AE profile in patients with and without renal impairment (Table V). The overall number of patients with AEs increased numerically with declining renal function, although the incidences of AEs, including fatal events, were similar for patients receiving linagliptin and placebo within each renal function subgroup. A similar pattern was observed for the incidence of hypoglycemic events by renal function (Figure D).

DISCUSSION

The findings of this updated and expanded post hoc pooled analysis of all currently available placebo-controlled trials of linagliptin (22 studies), which included a total of 7400 patients exposed to linagliptin or placebo, provides further evaluation of the overall safety profile of linagliptin. This analysis supports the findings of previous studies, showing that the safety profile for linagliptin is consistent with the adverse effects listed in the current prescribing information for linagliptin.[9] The subgroup analyses conducted show

Table IV. Summary of AEs by system organ class in overall population (TS).

AEs	Linagliptin (n = 4810)	Placebo (n = 2590)
Blood and lymphatic system disorders	(2.1)	(2.2)
Cardiac disorders*	153 (3.2)	85 (3.3)
Arrhythmia	4 (0.1)	2 (0.1)
Tachycardia	11 (0.2)	3 (0.1)
Cardiac events		
Acute coronary syndrome	3 (0.1)	2 (0.1)
Acute myocardial infarction	7 (0.1)	4 (0.2)
Angina pectoris	22 (0.5)	13 (0.5)
Unstable angina	4 (0.1)	4 (0.2)
Cardiac arrest	2 (<0.1)	0 (0.0)
Myocardial infarction	9 (0.2)	3 (0.1)
Myocardial ischemia	11 (0.2)	4 (0.2)
Silent myocardial infarction	1 (<0.1)	0 (0.0)
Narrow SMQ cardiac failure	21 (0.4)	8 (0.3)
Acute cardiac failure†	2 (<0.1)	0 (0.0)
Acute pulmonary edema†	1 (<0.1)	1 (<0.1)
Cardiac failure†	6 (0.1)	2 (0.1)
Cardiogenic shock†	1 (<0.1)	0 (0.0)
Congestive cardiac failure†	5 (0.1)	5 (0.2)
Left ventricular failure†	6 (0.1)	0 (0.0)
Pulmonary edema†	1 (<0.1)	2 (0.1)
Right ventricular failure†	1 (<0.1)	0 (0.0)
Congenital, familial, and genetic disorders	2 (<0.1)	1 (<0.1)
Ear and labyrinth disorders	50 (1.0)	28 (1.1)
Endocrine disorders	17 (0.4)	10 (0.4)
Eye disorders	158 (3.3)	87 (3.4)
Gastrointestinal disorders	548 (11.4)	33 (12.7)
Diarrhea	132 (2.7)	77 (3.0)
Pancreatitis	2 (<0.1)	1 (<0.1)
Chronic pancreatitis	3 (0.1)	0 (0.0)
General disorders and administration site conditions	286 (5.9)	181 (7.0)
Hepatobiliary disorders	42 (0.9)	23 (0.9)
Immune system disorders	14 (0.3)	10 (0.4)
Drug hypersensitivity	4 (0.1)	1 (<0.1)
Infections and infestations	1025 (21.3)	648 (25.0)
Influenza	80 (1.7)	60 (2.3)
Nasopharyngitis	281 (5.8)	155 (6.0)
Upper respiratory tract infection	159 (3.3)	111 (4.3)
Urinary tract infection	144 (3.0)	106 (4.1)
Injury, poisoning, and procedural complications	249 (5.2)	148 (5.7)
Investigations	260 (5.4)	167 (6.4)
Amylase increased	14 (0.3)	4 (0.2)
Metabolism and nutrition disorders	988 (20.5)	721 (27.8)
Hyperglycemia	319 (6.6)	330 (12.7)

(continued)

Table IV. (continued).

AEs	Linagliptin (n = 4810)	Placebo (n = 2590)
Hypoglycemia	532 (11.1)	349 (13.5)
Musculoskeletal and connective tissue disorders	540 (11.2)	315 (12.2)
Arthralgia	98 (2.0)	60 (2.3)
Back pain	118 (2.5)	79 (3.1)
Neoplasms benign, malignant, and unspecified	29 (0.6)	24 (0.9)
Pancreatic cancer	0 (0.0)	0 (0.0)
Nervous system disorders	389 (8.1)	248 (9.6)
Dizziness	114 (2.4)	64 (2.5)
Headache	148 (3.1)	85 (3.3)
Cerebral ischemia	1 (<0.1)	2 (0.1)
Cerebrovascular accident	4 (0.1)	3 (0.1)
Ischemic stroke	0 (0.0)	2 (0.1)
Transient ischemic attack	2 (<0.1)	2 (0.1)
Pregnancy, puerperium, and perinatal conditions	0 (0.0)	1 (<0.1)
Psychiatric disorders	87 (1.8)	76 (2.9)
Renal and urinary disorders	170 (3.5)	114 (4.4)
Reproductive system and breast disorders	55 (1.1)	45 (1.7)
Respiratory, thoracic, and mediastinal disorders	229 (4.8)	129 (5.0)
Cough	95 (2.0)	51 (2.0)
Skin and subcutaneous tissue disorders	217 (4.5)	131 (5.1)
Social circumstances[‡]	0 (0.0)	1 (<0.1)
Surgical and medical procedures	25 (0.5)	18 (0.7)
Vascular disorders[*]	182 (3.8)	114 (4.4)
Hypertension	113 (2.3)	73 (2.8)

AE = adverse event; TS = treated set.
Data are number (%).
Subcategories shown if incidence in either group was ≥2% or was a selected AE of interest. AEs are reported as system organ classes and preferred terms from the Medical Dictionary for Regulatory Activities (MedDRA) version 15.1.
[*]The System Organ Classes, cardiac disorders and vascular disorders are grouped by manifestation site. The cardiac disorders class includes conditions such as coronary artery disease, heart failure, arrhythmias, and valve disorders; vascular disorders includes hypo- and hypertension, deep venous thrombosis, peripheral arterial disease, and arteriosclerosis.
[†]These preferred terms are included in the standardized Medical Dictionary for Regulatory Activities query (SMQ) for heart failure.
[‡]Refers to 1 incidence of menopause reported in the placebo group.

that the safety and tolerability of linagliptin, including the risk of hypoglycemia, is not adversely affected by increasing age or declining renal function.

Overall, the reported AEs were of similar incidence for linagliptin- and placebo-treated patients (overall AEs, 57.3% and 61.8%, respectively), with similar incidences of serious AEs and drug-related AEs. Furthermore, there were no apparent differences between the linagliptin and placebo groups for the AEs that were most frequently reported, including infections, musculoskeletal disorders, nervous system disorders, and gastrointestinal disorders.

Given the similarity in AE profiles for linagliptin and placebo reported in this analysis and in previous studies,[16,18,19,41] some specific trends observed may likely be attributed to factors beyond the studied medication. For example, the relatively high frequency of infections across the population as a whole is

Table V. Frequency of investigator-reported AEs, including investigator-defined hypoglycemic events, by age (years) and renal function (eGFR), for linagliptin versus placebo (TS).

	Linagliptin	Placebo	Linagliptin	Placebo	Linagliptin	Placebo
	Age <65 y		Age 65–74 y		Age ≥75 y	
No.	3389	1789	1153	647	268	154
Any AE, no. (%)	1878 (55.4)	1062 (59.4)	700 (60.7)	427 (66.0)	180 (67.2)	112 (72.7)
Drug-related AEs	352 (10.4)	201 (11.2)	163 (14.1)	123 (19.0)	47 (17.5)	30 (19.5)
SAEs, no. (%)	141 (4.2)	81 (4.5)	68 (5.9)	59 (9.1)	21 (7.8)	27 (17.5)
Fatal events, no. (%)	7 (0.2)	5 (0.3)	3 (0.3)	2 (0.3)	0 (0.0)	2 (1.3)
No.	3389	1789	1153	647	268	154
Hypoglycemia, no. (%)	322 (9.5)	187 (10.5)	172 (14.9)	140 (21.6)	59 (22.0)	35 (22.7)
	eGFR ≥90		eGFR 60–90		eGFR <60	
No.	1918	955	2263	1198	619	422
Any AE, no. (%)	1035 (54.0)	545 (57.1)	1281 (56.6)	731 (61.0)	436 (70.4)	319 (75.6)
Drug-related AEs	167 (8.7)	89 (9.3)	270 (11.9)	161 (13.4)	125 (20.2)	101 (23.9)
SAEs, no. (%)	60 (3.1)	42 (4.4)	104 (4.6)	60 (5.0)	66 (10.7)	65 (15.4)
Fatal events, no. (%)	1 (0.1)	2 (0.2)	3 (0.1)	1 (0.1)	6 (1.0)	6 (1.4)
No.	1918	955	2263	1198	619	422
Hypoglycemia, no. (%)	159 (8.3)	71 (7.4)	235 (10.4)	157 (13.1)	159 (25.7)	133 (31.5)

AE = adverse event; eGFR = estimated glomerular filtration rate; SAE = serious adverse event; TS = treated set.
An SAE was defined as an event that was fatal or life-threatening, required in-patient hospitalization or prolonged existing hospitalization, resulted in persistent or significant disability/incapacity, was a congenital anomaly/birth defect, or was deemed serious for any other reason.

consistent with the presence of T2DM, and the frequency of diarrhea, a common side effect of metformin therapy, is consistent with the high level of background metformin therapy (alone or with other background therapies) used by the study participants (61.2% of linagliptin- and 54.7% of placebo-treated patients).

The incidence of hypoglycemia was low among patients receiving linagliptin and did not appear to increase, relative to placebo, by advancing age or declining renal function or by background insulin therapy. Interestingly, the overall incidence of investigator-defined hypoglycemic AEs was significantly lower with linagliptin therapy than for placebo. At present, the explanation for the significantly lower frequency of investigator-defined hypoglycemic events for linagliptin- versus placebo-treated patients is unclear. Further research is warranted to evaluate the similar incidence of hypoglycemia with linagliptin; conducting an analysis with exclusion of reports of hypoglycemic events after glycemic rescue therapy would be an appropriate initial approach. It is interesting to note that data from other incretin-based therapies indicate that this is likely to involve an enhancement of islet responsiveness (both α and β cell) to hypoglycemia,[42,43] potentially mediated through an increase in GIP levels.[44] However, it is also important to emphasize that the incidence of hypoglycemia is increased when linagliptin is given on a background of SU versus linagliptin plus placebo. This effect on hypoglycemia has been demonstrated with all incretin-based therapies and is thought to be due to a pharmacodynamic interaction whereby SU therapy uncouples the insulinotropic action of GLP-1 from its glucose dependence.[45] An increase in the risk of hypoglycemia is well known with SU therapy and an increase in hypoglycemic events has been reported when these agents are used in combination with other antihyperglycemic drugs, such as metformin

and GLP-1 agonists.[46,47] Adjustment of SU therapy to a lower dose should, therefore, be considered when adding linagliptin to pre-existing SU therapy. This is recommended in the prescribing information for linagliptin[9] and other DPP-4 inhibitors.[48,49]

Recent studies indicated a possible link between incretin-based therapies and an elevated risk of the development of acute pancreatitis or pancreatic cancer.[50,51] Pancreatitis is listed as an adverse reaction associated with linagliptin therapy, as listed in the prescribing information.[9] This is further emphasized in the product labeling, which states that treatment should be discontinued if pancreatitis is suspected. The present pooled post hoc analysis demonstrates a low incidence of pancreatitis and shows similar incidences of pancreatic malignancy with linagliptin therapy and placebo. The number of events in this patient population, however, is too small for in-depth safety evaluations of very rare events such as pancreatitis or cancer. It is likely that pharmacoepidemiological approaches will be needed to fully address this question.

A cardiovascular (CV) risk assessment of linagliptin has been performed in 2 prespecified analyses, both of which have not shown an increase in CV risk associated with linagliptin therapy.[52,53] Similarly, reassuring findings have emerged from the randomized CV outcome trials, EXAMINE (EXamination of CArdiovascular outcoMes: AlogliptiN versus Standard of carE in patients with type 2 diabetes mellitus and acute coronary syndrome) and SAVOR-TIMI 53 (The Saxagliptin Assessment of Vascular Outcomes Recorded in patients with diabetes mellitus [SAVOR] - Thromboloysis In Myocaridal Infadcrtion [TIMI]). EXAMINE was designed to investigate whether major CV event rates were higher with alogliptin compared with placebo therapy in patients with T2DM and recent acute coronary syndrome.[54] After a median follow-up period of 1.5 years, similar rates of major CV AEs in addition to CV or all-cause mortality were reported for patients allocated to alogliptin or placebo. The SAVOR-TIMI 53 trial evaluated the effects of saxagliptin on CV outcomes in T2DM patients at high CV risk. No difference in the primary composite endpoint of CV death, myocardial infarction, or ischemic stroke was found in saxagliptin- or placebo-treated patients.[55] An unexpected finding of this trial was an increased incidence of hospital admissions for chronic heart failure in patients receiving saxagliptin, whereas no difference in heart failure-related death was reported. Similarly, a trend toward an increased risk of hospital admission for chronic heart failure was also found in the EXAMINE trial.[56] These findings merit further evaluation. No apparent increased risk of heart failure with linagliptin was found in the current pooled analysis, although it is not possible to draw definitive conclusions from these data, as the number of events was small.

In view of the xanthine-based structure of linagliptin and the known relationship between other xanthine derivatives and cardiac effects such as tachycardia and arrhythmias, the impact of linagliptin therapy on these AEs is of interest. At present, there are no data to suggest an increased risk of these events with linagliptin therapy.

As with all pooled analyses, the present study is limited by the use of data from different clinical studies, as well as the relatively short duration of the included studies. In addition, no inferential statistics were derived, except for the analysis of hypoglycemia. However, this analysis was based on individual patient data from a consistently designed, large clinical development program, so methodological differences between individual trials were small. Furthermore, the use of pooled patient-level data provides a more sensitive evaluation of research findings than meta-analysis of trial-level data, which only reports whether an event has occurred in a trial. The robustness of the findings of the present study is further supported by the consistency of the results obtained across the individual trials.

The duration and timing of intervention, in addition to the presence of concomitant conditions and the stage of T2DM, likely influence outcomes in the management of patients with T2DM. Thus, ongoing trials have been uniquely designed to further evaluate the long-term safety and potential benefits of linagliptin in high-risk patient groups exhibiting a higher CV risk compared with the patients included in the present analysis. With regard to CV outcomes, the effect of linagliptin on CV endpoints is currently under evaluation in the CAROLINA® (CARdiovascular Outcome Study of LINAgliptin versus Glimepiride in Patients with Type 2 Diabetes trial) (NCT01243424), which includes patients with early T2DM identified as being at moderate risk of CV disease, with a proportion of these having previous CV disease. This is the only head-to-head CV outcome trial of a DPP-4 inhibitor versus active comparator that is sufficiently powered to assess CV events (targeting time to first occurrence of 631 CV death, non-fatal

stroke, non-fatal myocardial infarction or hospitalization for unstable angina).[57] A second cardiorenal outcome study, which started in the middle of 2013, the CARMELINA® (CARdiovascular Safety & Clinical outcoME with LINAgliptin) trial (NCT01897532), will compare the CV and renal safety of linagliptin versus placebo, when added to standard care in patients with T2DM at high CV risk. Adults with T2DM and evidence of renal impairment, with or without previous CV complications, or with albuminuria (urine albumin-to-creatinine ratio $\geq$30 mg/g) plus evidence of CV complications, will be randomized into the study. CARMELINA is the only study of DPP-4 inhibitors to explore both macrovascular (targeting 625 4P-major adverse cardiac events [4-component composite endpoint: CV death, stroke, myocardial infarction, or unstable angina pectoris with hospitalization]) and microvascular (targeting time to first occurrence of 625 CV death, non-fatal stroke, non-fatal myocardial infarction or hospitalization for unstable angina) endpoints, and its findings will provide important clinical guidance. Both of these studies will also assess the impact of linagliptin therapy on heart failure, and other important safety endpoints, including pancreatitis, malignancies, severe hypersensitivity reactions, and renal or hepatic AEs.

CONCLUSIONS

The findings of this updated and expanded, post hoc pooled analysis of all currently available placebo-controlled trials of linagliptin 5 mg daily support previous findings that have demonstrated an acceptable safety profile with respect to the overall safety and tolerability of linagliptin when administered to a broad range of patients with T2DM. In the present analysis, linagliptin-treated patients were shown to have a low overall incidence of hypoglycemia (although this incidence was increased by concomitant SU therapy). Furthermore, the tolerability of linagliptin did not appear to be altered by increasing age or decreasing renal function. The results of ongoing clinical trials, such as CAROLINA and CARMELINA, will provide additional insight into the long-term safety and tolerability of linagliptin.

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Dr. Johansen was responsible for the literature search, study design, data collection and interpretation, figure creation, and writing of the manuscript. Drs. Lehrke, Marx, Patel, Seck, Cheng, and Eynatten were responsible for the study design, data interpretation, and writing or the manuscript. Ms. Crowe was responsible for the data interpretation and writing of the manuscript.

CONFLICTS OF INTEREST

M. Lehrke has been a speaker/advisory panel member for the following companies: AstraZeneca, Boehringer Ingelheim, Bristol-Myers Squibb, GlaxoSmithKline, Merck Sharp & Dohme, and Roche. N. Marx has been a speaker/consultant for the following companies: Amgen, AstraZeneca, Bayer, Bristol-Myers Squibb, Boehringer Ingelheim, Cordis, Genfit, GlaxoSmithKline, Lilly, Merck Sharp & Dohme, Novartis, NovoNordisk, Pfizer, Roche, Sanofi-Aventis; and has received research grants from Boehringer Ingelheim and participated in clinical trials sponsored by Boehringer Ingelheim. The other authors have indicated that they have no other conflicts of interest regarding the content of this article.

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